REMARKS

Claims 6-13 and 19-43 are pending and are the subject of the present Office Action. For the Examiner's convenience, a clean copy of all the now pending claims 6-13 and 19-43 is provided above.

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Claims 6-13 and 19-43 were rejected under Section 103(a) as being unpatentable over US Patent 6,252,050 or WO98/51793 in view of Keane et al. and Rougier et al. Applicants respectfully traverse the rejection.

The present claims are directed to the use of synergistic or effective amounts of anti-DR5 agonist antibody and CPT-11, which Applicants unexpectedly found have a synergistic effect in inducing apoptosis in mammalian cancer cells. The art cited by the Examiner does not teach or suggest any reasonable expectation to those skilled in the art that such agents could be combined to achieve a synergistic effect in inducing apoptosis in mammalian cancer cells.

First, while Rougier et al. provides a very limited teaching regarding use of CPT-11 in clinical studies of colorectal cancer patients, the Rougier et al. abstract does not suggest to the skilled artisan that CPT-11 and 5-FU are comparable agents having identical activity or mechanism of action. Indeed, the abstract suggests otherwise. The statement that "CPT-11 appears to have activity similar to that of 5-FU in first-line treatment..." is in fact countered by the immediately preceding statement in Rougier et al. that "CPT-11 has shown promising antitumor activity in the treatment of patients with advanced colorectal cancer including those refractory to 5-fluorouracil (5-FU)-based regimens..." and the subsequent text stating ..."[CPT-11] remains active after failure of 5-FU therapy." (emphasis added) The present application even discloses on page 11, lines 25-28, that Camptostar®, the CPT-11 product, can be used for treatment of patients whose disease has recurred or progressed following 5-FU based therapy. Accordingly, Rougier et al. itself, and in view of the present application, establishes that CPT-11 and 5-FU

are not "one and the same" or interchangeable types of chemotherapy drugs and those skilled in the art readily understand as such.

Keane et al. describe certain experiments examining the combined effects of a GST-TRAIL protein construct and doxorubicin, 5-FU, paclitaxel, melphalen or methotrexate on selected cell lines. The data observed by Keane et al. is summarized in Table I on page 738 of the Keane et al. reference. Applicants respectfully point out that the data reported by Keane et al. not only fails to suggest employing CPT-11 in combination with TRAIL (or Apo-2 ligand), but fails to suggest that combinations of different chemotherapy agents and TRAIL have similar or predictable effects with regards to synergistic action. Indeed, Keane et al. teach the exact opposite.

On page 734 of the Keane et al. reference, Abstract at lines 14-16 and 19-22, Keane et al. teach:

> ...Incubation of cell lines with doxorubicin or 5-fluorouracil significantly augmented TRAIL-induced apoptosis in most breast cell lines...In contrast, melphalan and paclitaxel augmented TRAIL-induced apoptosis in a few cell lines, and methotrexate did not augment it in any cell line.

Thus, Keane et al. actually teach away from any expectation that another chemotherapy, such as CPT-11, would have any particular activity when used in combination with TRAIL (Apo-2 ligand) or an agonist antibody having apoptosis inducing activity similar to the ligand.

For these reasons, it is respectfully submitted that there is no motivation to combine the teachings of the cited references, and even if one were to try to do so, there is no reasonable expectation of the results. It is accordingly believed that the claimed invention is not obvious over the cited art, and withdrawal of the rejections is respectfully requested.

Respectfully submitted,

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